Theoretical Calculations of Extraction Selectivity: Alkali Cation Complexes of Calix[4]-bis-crown6 in Pure Water, Chloroform, and at a Water/Chloroform Interface

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ABSTRACT

We report theoretical calculations of ion extraction selectivity by ionophores, based on molecular dynamics simulations coupled with the free energy perturbation technique. This method is applied to the Calix[4]-bis-crown6 (L) ionophore, which displays remarkable selectivity for Cs^+ over Na^+ extraction from an aqueous to a chloroform phase. Using a thermodynamic cycle, we model the cation *extraction* selectivity of L from water to chloroform and calculate a peak for Cs^+, in agreement with the experiment. This high Cs^+ ionophoricity is accounted for mostly by differential solvation effects, with standard 1–6–12 pairwise potentials without need of "special π interactions" with the ionophore. The effect of a picrate (Pic^-) counterion on structures and selectivities is investigated. Finally, we report simulations on the L ionophore free and on the LCs^+ and LCs^+Pic^- complexes at the water/chloroform interface. We find that all these species are "adsorbed" at the interface like surfactants instead of diffusing spontaneously to the organic phase.

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Introduction

Solvent extraction is widely used in practice to concentrate and separate organic and inorganic substances, in particular salts of metals. Although a lot of experimental results on the extraction of metals are available (e.g., see the literature for monographs[1-4] and reviews[5-7]), there is still no consistent theoretical method to analyze the mechanism and thermodynamical parameters of this process at the microscopic level. This is related to the complexity of studied systems where metal cations, counterions, and molecules of extractant are partitioned between two liquid phases. The organic phase is not "dry" but usually contains some amount of water that is either dissolved in the organic solvent or transferred there together with the metal salt.

Attempts have been made to correlate the extraction selectivity with empirical indices of the extractant molecules without taking into account explicitly the complex formed, the solvent, or the dynamical features of the complex. For instance, the metal extraction selectivity of neutral phosphoryl-containing ligands has been analyzed on the basis of gas phase calculations of the extractants and their metal complexes. Various parameters related to the electronic structure of the free ligands have been used to interpret the experimental data: electronegativities of substituents in P=O groups, atomic charges, protonation energies,[7] electrostatic potential distribution,[8,9] and chemical "hardness" and "softness" calculated either empirically[6] or by quantum mechanics methods.[10] For the complexes with actinides, donor–acceptor interactions have been calculated.[10] Although a linear correlation between extraction constants of the ionophores and some of the above mentioned indices was observed, no firm conclusions were drawn because solvent effects were not taken into consideration.

More sophisticated molecular dynamics (MD) and free energy perturbation (FEP) studies on alkali cation complexes of crown ethers,[11,12] cryptands,[13,14] cavitands,[15] and calixarenes[16-22] in water or in methanol involved an explicit representation of the solvent, using an empirical force field instead of a quantum mechanics representation of the system. These studies addressed the question of *complexation* selectivities in pure homogeneous solvents (see also refs. 23–26 and references cited therein).

Using the FEP technique, Jorgensen et al.[27] calculated the relative free energies of transfer of small neutral organic solutes from water to the organic phase. This is a somewhat different situation from extraction of cations by ionophores, because in the latter case formation of a complex is involved.

In this article we present a method to calculate extraction selectivities of metals by ionophores using MD simulations coupled with the FEP technique.[26,28] It is applied on the calix-bis-crowns-6 ligand (**L**) that displays a high Cs^+/Na^+ selectivity in extraction of alkali cations from water to a (2-nitrophenyl)octylether solution.[29,30] This ionophore belongs to a new family of highly preorganized calix[4]-bis-crown host molecules[31-33] where the aromatic core is locked in the *1,3-alternate* conformation by two bridging polyether chains (Fig. 1). Dialkoxy-calix[4]-crown6 ligands, the analogue of **L**, selectively extract Cs^+ from water to chloroform.[34] The high Cs^+ selectivity of calix[4]-crown6 and calix[4]-bis-crown6 is of particular interest in the context of Cs^+ decontamination in nuclear wastes,[30,35] but is not clearly understood in terms of cation–ligand interactions, solvation, and possible counterion effect. In cation extraction experiments, the selectivity is generally discussed in terms of the free energy of complexation in the organic phase. According to this approach, calix[4]arene-bis-crown6 would complex Cs^+ better than Na^+ in the organic phase.[34,36,37]

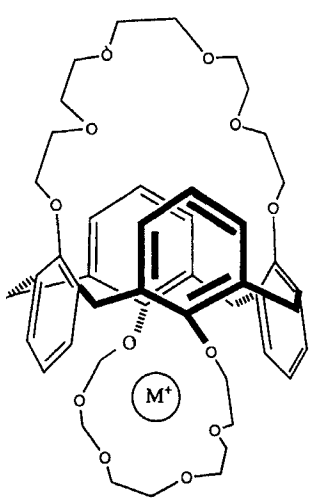

FIGURE 1. M^+ complexes of calix[4]-bis-crown6.

Recently we addressed the question of cation complexation selectivity of several calix[4]-bis-crown hosts in pure solvents (water, methanol, acetonitrile, and chloroform) as a function of size of the cavity (calix[4]-bis-crown5 or calix[4]-bis-crown6), of H vs. *t*-butyl substituents at the para positions, and of the presence of Pic^- counterion.[20] The results reported in ref. 20 focused mostly on the structural features of the complexes, on the solvation pattern in different solvents, and on the cation complexation selectivity of calix[4]-bis-crowns in pure homogeneous solution. The work reported here is devoted to the problem of Cs^+/Na^+ *extraction* selectivity by calix[4]-bis-crown6 with the following items in mind: the relative free energies of extraction of cations by **L** from water to chloroform; the relationship between extraction selectivity of a given ionophore with its complexation selectivity in the source (water) or in receiving (organic) phases; the role of counterions in extraction of metals; the structure of the LM^+ and LM^+Pic^- complexes in water, compared to the organic phase; and mechanistic features concerning the cation–ligand complexation. In particular, it is not clear whether complex formation takes place in water, in the organic phase, or at the interface.

We chose chloroform to model the organic phase because it is a good representative of organic apolar solvents used in ion extraction experiments[3]; and to our knowledge, so far it has not been considered computationally for ionophoric systems. Calculations in pure chloroform serve also as a reference for the studies at the water/chloroform interface reported here.

Finally, in relation with the cation extraction of cations by calix-bis-crowns from water to an organic phase, we report the first MD simulations of calix[4]-bis-crown6 and its complexes with Cs^+ and Cs^+Pic^- at a water/chloroform interface represented explicitly.

Computation Procedure

MD calculations were performed with AMBER4 software.[38] The parameters for intramolecular and nonbonded intermolecular interactions are taken from ref. 39. Alkali cations are represented by the Åqvist parameters.[40] Atomic charges on the atoms of polyether fragments ($q_o = -0.404$, $q_C = 0.244$, and $q_H = -0.021$) are taken from ref. 41, and for the $R—C_6H_2—CH_2$ aromatic fragments we used charges calculated by the Gasteiger and Marsili method[42] as in the study of calix[4]-crown M^+ complexes.[21] For the picrate anion, we used the MNDO ESP charges from Troxler and Wipff[43] (Fig. 2) with a torsional V_2 terms of 2.9 kcal/mol for the CC—NO dihedrals.

The solvent parameters are derived from pure liquid simulations (OPLS parameters for $CHCl_3$,[27] and the TIP3P potentials for water[44]).

The starting structures for calix-bis-crown6 and its complexes were built using MacroModel.[45] For the simulations in solution, the solute was placed at the center of a solvent rectangular box of about 32–35 Å length, containing 829 H_2O or 200–250 $CHCl_3$ molecules. The simulations at the water–chloroform interface were performed with 900–1100 H_2O and 280–350 $CHCl_3$ molecules. The calculations were performed at constant volume in nonaqueous solutions and in two-phase systems. In water solution a constant pressure of 1 atm was used. The residue based cutoff for nonbonded interactions was set to 10 Å in water and 12 Å for the simulations in pure chloroform and at the chloroform/water interface, using periodic boundary conditions. After 1000 steps of conjugate gradient minimization, the system was equilibrated for 5 ps of MD at 300 K starting with random velocities. This was followed by 100–550 ps of MD. The Verlet algorithm was used with a time step of 2 fs

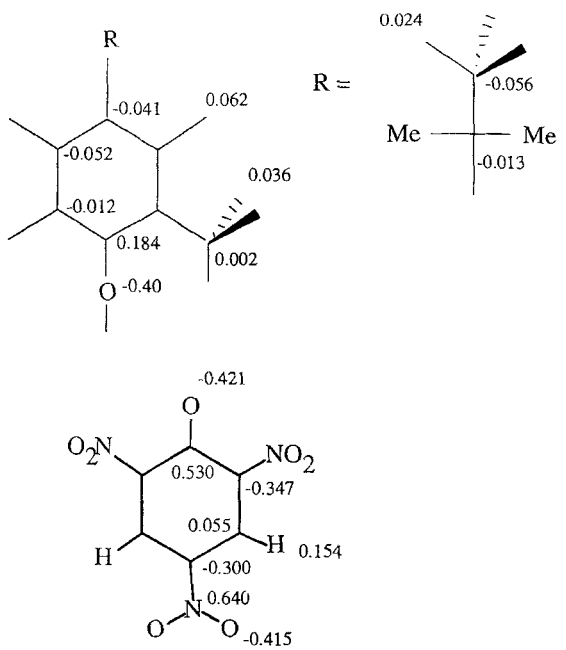

FIGURE 2. Charge distribution of the calix[4]-bis-crown6.

in conjunction with SHAKE to constrain all covalent bonds involving an H atom, and the Cl—Cl and C—Cl bonds of chloroform to their equilibrium length. The temperature was maintained at 300 K by velocity scaling in the gas phase, and by coupling to a thermal bath in solution using a relaxation time of 0.1 ps.

The differences in free energies between LM_1^+ and LM_2^+ complexes or between the free M_1^+ and M_2^+ cations were calculated using the statistical perturbation FEP theory[46] and the windowing technique, with the same protocol as described in ref. 20.

Results

The structural features of the LCs^+ and LCs^+Pic^- complexes have been described in detail in ref. 20. Of particular interest was the nice fit between Cs^+ and the crown cavity of **L** in water as in chloroform, with or without Pic^- counterion. This contrasted with the versatile behavior of Na^+ inside the host. Indeed, depending on the nature of solvent and on the presence of the counterion, Na^+ could sit either deeply inside the calixarene near phenolic oxygens (*endo* position) or bind mostly to the oxygens of the polyether bridge (*exo* position). In the following, we therefore focus on energy features related to cation *extraction* selectivity. Complexation results reported in ref. 20 are considered here for the purpose of discussion and comparison.

RELATIVE FREE ENERGIES OF EXTRACTION FROM FEP SIMULATIONS

In our previous study[20] the complexation selectivity of ionophores in pure homogeneous solvent **S** was modeled using the thermodynamic cycle[28,46-48] presented in Scheme 1. The binding selectivity $\Delta\Delta G_c$ for complexing M_1^+ versus M_2^+, measured experimentally by $\Delta G_{c1} - \Delta G_{c2}$ was calculated as $\Delta G_{3,s} - \Delta G_{4,s}$.[11,49-52]

$$\Delta\Delta G_c = \Delta G_{c1} - \Delta G_{c2} = \Delta G_{3,s} - \Delta G_{4,s}. \quad (1)$$

$$\begin{array}{ccc} (\mathbf{L} + M_1^+)_s & \xrightarrow{\Delta G_{c1}} & (LM_1^+)_s \\ {\scriptstyle \Delta G_{3,s}}\downarrow & & \downarrow{\scriptstyle \Delta G_{4,s}} \\ (\mathbf{L} + M_2^+)_s & \xrightarrow[\Delta G_{c2}]{} & (LM_2^+)_s \end{array}$$

SCHEME 1. Thermodynamic cycle used to analyse the *complexation* selectivity of M_1^+/M_2^+ by **L** in a solvent **s**.

$$\begin{array}{ccc} \mathbf{L}_{org} + M_{1wat}^+ & \xrightarrow{\Delta G_{ex1}} & (LM_1^+)_{org} \\ {\scriptstyle \Delta G_{3,org}}\downarrow & & \downarrow{\scriptstyle \Delta G_{4,org}} \\ \mathbf{L}_{org} + M_{2wat}^+ & \xrightarrow[\Delta G_{ex2}]{} & (LM_2^+)_{org} \end{array}$$

SCHEME 2. Thermodynamic cycle used for the analysis of the *extraction* selectivity of M_1^+/M_2^+ by **L** from water to an organic solvent.

Here we model the selectivity for extraction of M^+ ions from an aqueous to an organic (chloroform) solution, using the thermodynamic cycle presented in Scheme 2.

This model assumes that the free ions are present in water only, while the complexes are entirely in the organic phase. The selectivity of extraction is given by

$$\Delta\Delta G_{ex} = \Delta G_{ex1} - \Delta G_{ex2} = \Delta G_{3,wat} - \Delta G_{4,org}. \quad (2)$$

The problem arises in obtaining a realistic calculation of $\Delta G_{4,org}$ because in practice, the organic phase is not pure, but saturated with water. The concentration of water in this phase depends on the solvent, the extractant, and on the salts and can be comparable to, or larger than the concentration of the extractant **L**.[53] Locally this water concentration may be still larger.[55] For simplification, two extreme cases will be considered to estimate $\Delta G_{4,org}$. The first one corresponds to a high concentration of water in the organic phase where the solute is surrounded by water molecules. In this case,

$$\Delta G_{4,org} \approx \Delta G_{4,wat} \quad (3)$$

and hence,

$$\Delta\Delta G_{ex} \approx \Delta\Delta G_{c,wat}, \quad (4)$$

i.e., $\Delta\Delta G_{ex}$ is close to the differences in free energies of complexation in pure water solution.

The second extreme concerns the dry organic solvent that may be modeled explicitly. In this dry solvent, the anion can be taken into consideration as shown in Scheme 3. In that case the selectivity

$$\begin{array}{ccc} \mathbf{L}_{org} + (M_1^+)_{wat} + (Anion^-)_{wat} & \xrightarrow{\Delta G_{ex1}} & (LM_1^+Anion^-)_{org} \\ {\scriptstyle \Delta G_{3,wat}}\downarrow & & \downarrow{\scriptstyle \Delta G_{4,org}} \\ \mathbf{L}_{org} + (M_2^+)_{wat} + (Anion^-)_{wat} & \xrightarrow[\Delta G_{ex2}]{} & (LM_2^+Anion^-)_{org} \end{array}$$

SCHEME 3. Thermodynamic cycle used to analyse the M_1^+ $Anion^-/M_2^+$ $Anion^-$ *extraction* selectivity by **L** from water to an organic solvent.

of extraction is given by eq. (2) with $\Delta G_{4,org} = \Delta G_{4,chl}$.

Using the calculated $\Delta G_{3,wat}$, $\Delta G_{4,wat}$, and $\Delta G_{4,chl}$ energies leads to relative free energies $\Delta\Delta G_{ex}$ of cation extraction via the LM^+ and the LM^+Pic^- complexes given in the Table I. We find that both values of $\Delta\Delta G_{ex}$, calculated either in the water saturated or in the dry organic phase without counterion, predict the *selective extraction of* Cs^+ *versus* Na^+. Calculations performed in the presence of the counterion find the same Cs^+/Na^+ extraction selectivity, in full agreement with the experiment.[29,30]

Some quantitative differences in $\Delta\Delta G_{ex}$ are found that depend on which model is used to evaluate $\Delta G_{4,org}$ (Table I), suggesting that the concentration of water in the organic phase may modify the selectivity of extraction. Indeed, when the organic phase is "waterlike" ($\Delta G_{4,org} = \Delta G_{4,wat}$), the order of selectivity is $Cs^+ \geq Rb^+ \approx K^+ > Na^+$; while for the dry organic phase ($\Delta G_{4,org} = \Delta G_{4,chl}$), it is $Cs^+ \gg Rb^+ > K^+ > Na^+$.

SOLVATION AND DYNAMICS OF L, LCs^+ AND LCs^+Pic^- AT THE WATER/CHLOROFORM INTERFACE

We performed a series of MD experiments on L, LCs^+ and LCs^+Pic^- at the water/chloroform interface to determine to what extent the solute moves to one phase or the other, and to compare solvation and complexation at the interface and in the corresponding pure homogeneous phases. Given the high Cs^+ extraction observed experimentally, it could indeed be anticipated that these systems would migrate spontaneously to bulk chloroform. This is not the case.

Figure 3 schematically represents the two boxes of solvent and the interface. The free ligand L was initially placed at the center the interface, equally shared by the two solvents, with its pseudo-C_2 symmetry axis lying at the interface. The MD simulation was run for 550 ps. We found that the solute slowly diffuses to the organic phase, dragging several water molecules with one of them bridging two opposite ether oxygens of the crown

TABLE I.
Calculated Relative Free Energies (kcal/mol) of Na^+, K^+, Rb^+, and Cs^+ Uncomplexed and Complexed by L.

	$Na^+ \rightarrow K^+$	$K^+ \rightarrow Rb^+$	$Rb^+ \rightarrow Cs^+$	$Na^+ \rightarrow Cs^+$
Formation of LM^+ complexes in water[a]				
$\Delta G_{4,wat}$	14.8	5.0	6.5	26.3
$\Delta G_{3,wat}(M^+)$	17.6	5.1	7.7	30.4
$\Delta\Delta G_{c,wat}$	2.8	0.1	1.2	4.1
Formation of LM^+ complexes in chloroform[a]				
$\Delta G_{4,chl}$	9.7	4.7	6.1	20.5
$\Delta G_{3,chl}(M^+)$	2.3	2.0	0.9	5.2
$\Delta\Delta G_{c,chl}$	−7.4	−2.7	−5.2	−15.3
Formation of LM^+Pic^- complexes in chloroform[a]				
$\Delta G_{3,chl}$	11.6	4.0	6.6	22.2
$\Delta G_{3,chl}(M^+Pic^-)$	9.8	3.2	4.6	17.6
$\Delta\Delta G_{c,chl}$	−1.8	−0.8	−2.0	−4.6
Extraction of M^+ by L from water to chloroform				
$\Delta\Delta G_{ex}$[b]	7.9	0.4	1.6	9.9
$\Delta\Delta G_t^{complex}$[c]	5.1	0.3	0.4	5.8
$\Delta\Delta G_t^{cat}$[d]	15.3	3.1	6.8	25.2
Extraction of M^+Pic^- by L from water to chloroform				
$\Delta\Delta G_{ex}$[e]	6.0	1.1	1.1	8.2

[a] For a given solvent S (water or chloroform), the relative free energies $\Delta G_{3,s}$, $\Delta G_{4,s}$ and the relative free energies of complexation $\Delta\Delta G_{c,s}$ are defined by Scheme 1 and eq. (1) (see text and Schemes 1–6 for other definitions).
[b] Difference in free energies of M_1^+/M_2^+ extraction by L from water to chloroform: $\Delta\Delta G_{ex} = \Delta G_{3,wat} - \Delta G_{4,chl}(LM^+)$.
[c] Difference in free energies of transfer of LM_1^+/LM_2^+ complexes from water to chloroform: $\Delta\Delta G_t^{complex} = \Delta G_{4,wat} - \Delta G_{4,chl}$.
[d] Difference in free energies of transfer of $M_1^+M_2^+$ cations from water to chloroform: $\Delta\Delta G_t^{cat} = \Delta G_{3,wat} - \Delta G_{3,chlor}$.
[e] Difference in free energies of $M_1^+Pic^-/M_2^+Pic^-$ extraction by L from water to chloroform: $\Delta\Delta G_{ex} = \Delta G_{3,wat} - \Delta G_{4,chl}(LM^+Pic^-)$.

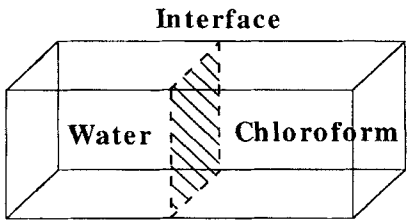

FIGURE 3. Schematic representation of the water / chloroform interface.

cavity (Fig. 4). However, it remains somewhat anchored at the interface without fully migrating to the bulk chloroform.

For the LCs^+ complex, two MD simulations of 100 ps were performed with different starting positions: LCs^+ was either at the interface as for the free L, or fully in the chloroform phase (near the center of the chloroform box). In fact, these two simulations end up with a similar situation where LCs^+ locates at the interface in an unsymmetrical arrangement. The polar Cs^+ crown ether part sits in contact with the aqueous phase, while the empty crown and aromatic frameworks are mostly in the chloroform phase (Fig. 5).

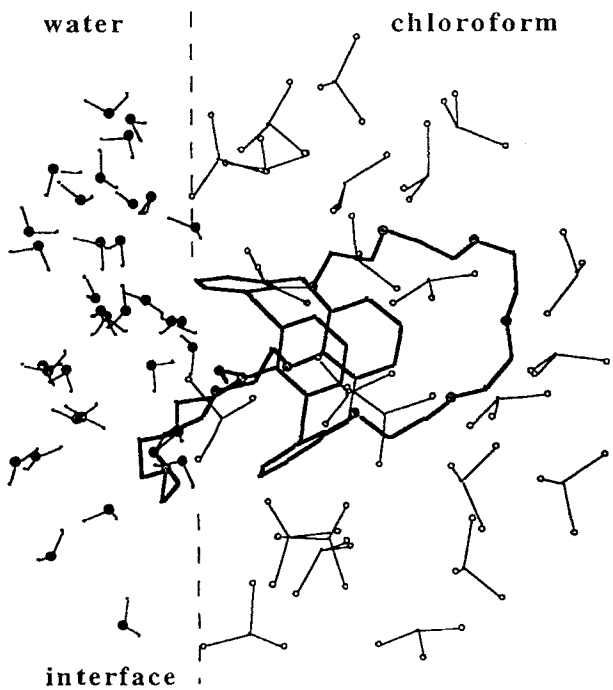

FIGURE 4. L free at the chloroform / water interface including selected solvent molecules. Snapshot after 100 ps of MD.

For the LCs^+Pic^- complex, we also performed two MD experiments MD1 and MD2, where the solute sits at the interface, but with different orientations and locations of Pic^-. Two different situations are observed. In the MD1 case, the complex LCs^+ and Pic^- were initially equally shared by the two solvents. In fact, it breaks completely and dissociates in 2 ps after the beginning of simulations: Cs^+ diffuses to the bulk water, while the ligand and the anion stay at the interface with loose contacts. The experiment MD2 starts with the complex at the interface such that Cs^+ and Pic^- are immersed in chloroform and the empty crown cavity is in water (Fig. 6). During the 200 ps of MD simulation, the Cs^+ crown cavity and Pic^- rotated to water, followed by the dissociation of the Pic^- counterion from the complex. The whole system remained, however, at the interface (Fig. 6).

The difference between MD1 and MD2 results demonstrates the importance of the starting configuration and the equilibration protocol. It is indeed remarkable that the LCs^+ complex, found to be the inclusive type in bulk water or in bulk chloroform solutions,[20] dissociates at the interface in MD1 where Cs^+ is captured by water. In the MD2 simulation, solvent relaxation around the solute at the interface stabilizes the Cs^+ complex after dissociation of the counterion.

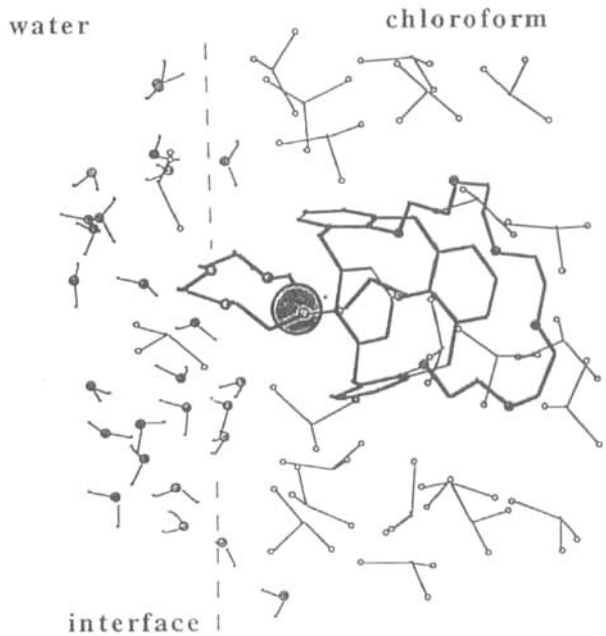

FIGURE 5. LCs^+ at the chloroform / water interface. Snapshot after 100 ps of MD.

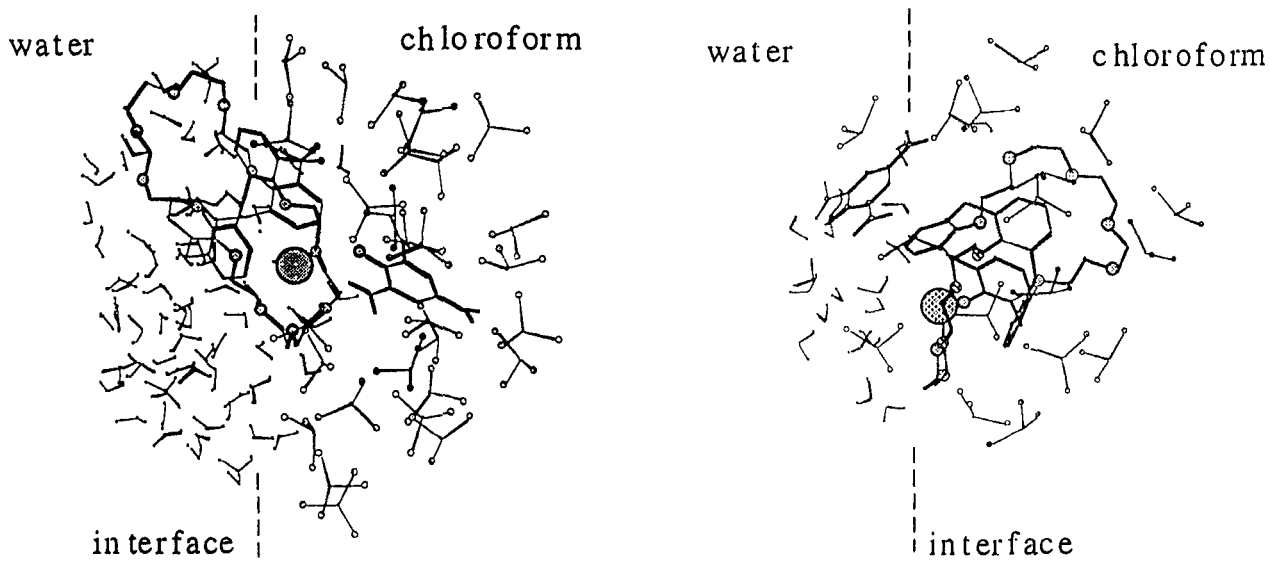

FIGURE 6. LCs^+Pic^- at the chloroform / water interface. Photos after 1 ps (left) and 200 ps (right) of MD.

Discussion

Na^+/Cs^+ COMPLEXATION AND EXTRACTION SELECTIVITY BY Calix[4]-bis-crown6: DOES EXTRACTION SELECTIVITY CORRELATE WITH COMPLEXATION SELECTIVITY IN THE SOURCE (WATER) OR RECEIVING (CHLOROFORM) PHASES?

According to the lock-and-key complementarity rule,[56-58] a macrocyclic ligand selectively binds cations that fit its cavity best. In terms of structural fit, it is clear that Na^+ is too small for the calix[4]-bis-crown6 simulated here, while Cs^+ best fits its size. Solvation effects also contribute to the binding selectivities.

The complexation selectivity in solution, measured by $\Delta\Delta G_c$, [see Scheme 1 and eq. (1)] is a function of the binding and solvation of the complexed cation (via ΔG_4), and of the cation desolvation energies (via ΔG_3). We calculate[20] that in water, **L** selectively binds Cs^+ ($Cs^+ > Rb^+ \approx K^+ > Na^+$), whereas in *pure* chloroform it prefers Na^+ ($Na^+ > K^+ > Rb^+ > Cs^+$). This seems in contradiction with the interpretation of related extraction data, which ascribed the Cs^+ peak to a more favorable free energy of binding in the organic phase.[34,59]

In the following, we analyze the question of extraction selectivity on the basis of the ionophore partition and the cation partition models.[5,54,60,61]. We derive a relationship between extraction selectivity of a given ionophore with its complexation selectivity in the source (water) or in receiving (organic) phases.

The thermodynamic cycle corresponding to the ionophore partition model is presented in Scheme 4.

According to Scheme 4, the relative free energy of extraction of cations M_1^+ and M_2^+ ($\Delta\Delta G_{ex}$) splits into two components corresponding to complex formation in water ($\Delta\Delta G_{c,wat}$) and to the transfer of the LM^+ complexes from water to the organic phase ($\Delta\Delta G_t^{complex}$)

$$\Delta\Delta G_{ex} = \Delta\Delta G_{c,wat} + \Delta\Delta G_t^{complex}, \qquad (5)$$

where $\Delta\Delta G_{c,wat}$ is calculated according to the Scheme 1. The differences in free energies of transfer of two complexes $\Delta\Delta G_t^{complex}$ can be computed by formula (6), as it was done to evaluate partition coefficients of organic molecules.[27,62]

$$\begin{aligned}\Delta\Delta G_t^{complex} &= \Delta G_{1,t}^{complex} - \Delta G_{2,t}^{complex} \\ &= \Delta G_{4,wat} - \Delta G_{4,org}. \end{aligned} \qquad (6)$$

In the present case of Cs^+/Na^+ extraction selectivity by **L**, Table I shows that neither $\Delta\Delta G_{c,wat}$ nor

$$\begin{array}{ccccc} (L)_{wat} + (M_1^+)_{wat} & \xrightarrow{\Delta G_{c1,wat}} & (LM_1^+)_{wat} & \xrightarrow{\Delta G_{1,t}^{complex}} & (LM_1^+)_{org} \\ \downarrow \Delta G_{3,wat} & & \downarrow \Delta G_{4,wat} & & \downarrow \Delta G_{4,org} \\ (L)_{wat} + (M_2^+)_{wat} & \xrightarrow[\Delta G_{c2,wat}]{} & (LM_2^+)_{wat} & \xrightarrow[\Delta G_{2,t}^{complex}]{} & (LM_2^+)_{org} \end{array}$$

SCHEME 4. Thermodynamic cycle used to analyse the M_1^+/M_2^+ *extraction* selectivity by **L** from water to an organic solvent within the *Ionophore Partition model.*

$\Delta\Delta G_t^{complex}$ components can be neglected because they contribute almost equally (4.1 and 5.8 kcal/mol, respectively) to $\Delta\Delta G_{ex}$ (9.9 kcal/mol). However, in this case the order of extraction selectivity and complexation selectivity in water are nearly the same. Such a correlation between extraction and complexation selectivities is not general. For instance, the anionic ligand dimethylglyoxymate$^-$ forms less stable complexes in water with Ni^{2+} than with Cu^{2+} (log K_s are 17.24 and 19.24, respectively).[6] However, Ni^{2+} is extracted better than Cu^{2+} (log K_{ex} are 1.0 and -0.4, respectively).

Let us now consider the thermodynamic cycle for the cation partition model (Scheme 5). It allows one to split $\Delta\Delta G_{ex}$ into the free energy of complexation in the organic phase ($\Delta\Delta G_{c,org}$) and the free energy of transfer of the cation M^+ from water to the organic phase ($\Delta\Delta G_t^{cat}$)

$$\Delta\Delta G_{ex} = \Delta\Delta G_{c,org} + \Delta\Delta G_t^{cat}, \quad (7)$$

where

$$\Delta\Delta G_t^{cat} = \Delta G_{1,t}^{cat} - \Delta G_{2,t}^{cat} = \Delta G_{3,wat} - \Delta G_{3,org}. \quad (8)$$

Counterion effects can be accounted for in eqs. (4) and (5) by replacement of (M^+) with (M^+Anion$^-$).

Calculations of $\Delta\Delta G_{ex}$ according to formulae (7)–(8) show that the contributions of the relative free energies of complexation in chloroform $\Delta\Delta G_{c,org} = \Delta\Delta G_{c,chl}$ are negative and much smaller by their absolute values than relative energies of transfer of the *free cations* from water to chloroform $\Delta\Delta G_t^{cat}$ (Table I). As expected, Cs^+ is more easily transferred than Na^+ ($\Delta\Delta G_t^{cat}$ = 25.1 kcal/mol). On the other hand, in chloroform, complexation of Na^+ is favored over Cs^+ complexation ($\Delta\Delta G_{c,chl} = -15.2$ kcal/mol). Thus, the extraction selectivity for Cs^+ results from the compromise between these two opposite effects.

Thus, both analyses, based either on the ionophore partition model or the cation partition model, lead to complementary views on the Cs^+/Na^+ extraction selectivity.

$$\begin{array}{ccccc} (L)_{org} + (M_1^+)_{wat} & \xrightarrow{\Delta G_{1,t}^{cat}} & (L)_{org} + (M_1^+)_{org} & \xrightarrow{\Delta G_{c1,org}} & (LM_1^+)_{org} \\ \downarrow \Delta G_{3,wat} & & \downarrow \Delta G_{3,org} & & \downarrow \Delta G_{4,org} \\ (L)_{org} + (M_2^+)_{wat} & \xrightarrow[\Delta G_{2,t}^{cat}]{} & (L)_{org} + (M_2^+)_{org} & \xrightarrow[\Delta G_{c2,org}]{} & (LM_2^+)_{org} \end{array}$$

SCHEME 5. Thermodynamic cycle used to analyse the M_1^+/M_2^+ *extraction* selectivity by **L** from water to an organic solvent within the *Ion Partition model*.

INFLUENCE OF COUNTERION ON EXTRACTION SELECTIVITY

We consider two aspects of counterion effects on the extraction selectivity. The first one is related to modeling of the extraction of salts with a given anion (Pic^- in our case). Is it necessary to account explicitly for the anion as in Scheme 3 or can we neglect it as in most of the calculations of cation complexes which have been performed so far? The second aspect concerns extraction experiments of a given cation with different counterions.

Extraction of Salts with a Same Anion

In polar protic solvents (water, methanol) or in polar aprotic solvents, at low salt concentrations, the cation and anion are separated and well solvated.[63] This is in agreement with results of simulations on M^+Pic^- ion pairs that dissociate in water in a few picoseconds[43] but remain intimate in chloroform. Therefore, modeling the complexation of alkali cations in water does not require, to a first approximation, accounting explicitly for the counterions. At low salt concentrations counterions can hardly effect ΔG_3 and ΔG_4 values in water (Scheme 3).

In chloroform, the ions are poorly solvated, and the salts are nearly insoluble, forming intimate ion pairs or aggregates.[63] It is clear that in dry chloroform the ligand would interact with the ion pair rather than with the cation alone. Therefore, the ΔG_3 and ΔG_4 free energies (Scheme 3) may be anion dependent. In the case of salts insoluble in chloroform, such interactions can be considered near the surface of the solid salt.[64] From a structural point of view, the comparison of LM^+ and LM^+Pic^- complexes in the gas phase or in chloroform shows that the anion "pulls" M^+ out of the cavity, particularly for small cations.[20] Thus in the LNa^+ complex, Na^+ is endo coordinated; and in the LNa^+Pic^- complex, it occupies an exo position.

Because the counterion can perturb the structure of the LM^+ complexes in the organic phase, it may quantitatively modify the cation extraction affinity via the ΔG_4 energy component. Such an effect is consistent with the experimental observations that, with most counterions, 18-crown-6 and and dibenzo-18-crown-6 extract K^+ better than other alkali cations,[65] but they selectively extract Cs^+ when a cobalt-containing soft counteranion is used.[66]

In our FEP calculations with or without picrate counterion, we found the same order of extraction selectivity (Table I), but the values of $\Delta\Delta G_{ex}$ are somewhat lower in LNa^+Pic^- than in the LM^+ complex. To conclude this section, it is clear that counterions may quantitatively modulate the Na^+/Cs^+ extraction and complexation selectivity but not inverse it, because we arrived at the same conclusion with or without Pic^- counterion.

Extraction of a Given Cation with Different Anions

The thermodynamic cycle described in Scheme 6 can be used to analyze the extraction selectivity of salts containing the same cation M^+ and different anions $Anion_1^-$ and $Anion_2^-$ using a same ligand **L**.

It follows from Scheme 6 that the anion may contribute both to $\Delta G_{3,wat}$ and to $\Delta G_{4,org}$. Because in water, ion pairs are dissociated, $\Delta G_{3,wat}$ corresponds to differences in free energies of hydration between the two anions. For the organic phase, $\Delta G_{4,org}$ corresponds either to differences in solvation energies of free anions (if they are fully dissociated from the complex) or to the differences in free energies between the two LM^+Anion^- complexes (when the anions remain paired with LM^+).

No data are available to our knowledge for calixarene complexes, but related counterion effects have been reported for other macrocyclic complexes. Thus, in extraction of K^+Hal^- ($Hal^- = F^-, Cl^-, Br^-, I^-$) by dibenzo-18-crown-6 from water to *m*-cresol, the partition coefficient (D_{M^+}) of M^+ decreases in the order $F^- > Br^- > I^- > Cl^-$,[67] which does not simply follow the relative order of dehydration free energies, i.e., $\Delta G_{3,wat}$.[68] Similar observations were reported by Olsher et al.[69] where the selectivity order of extraction of alkali cations by dicyclohexyl-18-crown-6 from water to chloroform does not correlate simply with the anion radii, hydration enthalpy, or softness parameters. The above results show that the counterion effects on selectivity cannot be related only to the differences between free energies $\Delta G_{3,wat}$. The anion

$$\begin{array}{ccc} L_{org} + (M^+)_{wat} + (Anion_1^-)_{wat} & \xrightarrow{\Delta G_{ex1}} & (LM^+Anion_1^-)_{org} \\ \Delta G_{3,wat}\downarrow & & \downarrow\Delta G_{4,org} \\ L_{org} + (M^+)_{wat} + (Anion_2^-)_{wat} & \xrightarrow[\Delta G_{ex2}]{} & (LM^+Anion_2^-)_{org} \end{array}$$

SCHEME 6. Thermodynamic cycle used to analyze the M^+ extraction by **L** from water to an organic solvent, with two different counterions.

modulated difference in structures of the LM^+Anion^- complexes also modulate $\Delta G_{4,org}$.

The calculations reported here and in previous comparisons of Cl^- and Pic^- counterions,[43] emphasize these two complementary aspects of this anion effect.

DYNAMICS OF IONOPHORES FREE AND COMPLEXED AT A WATER/CHLOROFORM INTERFACE

We report MD simulations at a water/organic interface, with a consistent comparison of the ionophore free, complexed with or without counterion. In all cases, the interface remains molecularly sharp (a few angstroms), as found in related simulations.[70-74]

Concerning the free ionophore, we observe some migration from the interface to chloroform, accompanied by a few water molecules bound to its crown ether. This is consistent with the known tendency of crown ethers to solubilize water in organic solvent, and the near insolubility of these calixarene ligands in water.[75]

The LM^+ complex remains at the interface with the polar cationic sites immersed in water, and the remaining less polar fragments immersed in chloroform. This was found independently of the initial orientation of the solute.

Two experiments were performed on the complexed ionophore in contact with the counterion. As observed without counterion, no spontaneous diffusion of this complex to the organic phase is observed. A similar "stationary state" was observed from Monte Carlo simulations on quaternary ammonium chlorides at the CCl_4/water interface, where the salts were efficiently solvated, but also remained at the interface.[76] Conversely we found that, once the complexed cation sits in the organic phase, it does not diffuse back to water, but clearly favors water diffusion into the organic phase. These results suggest that diffusion of the free ligand and of the complexed cation from water to the organic phase are not simple downhill energy processes, but involve an energy barrier that is not overcome spontaneously during these simulations. Larger time scales than the ones simulated here may be required. It may also be speculated that entropy effects related to solvent reorganization, to differential solvation of the solutes in both phases, and to concentration of the salt and carrier in the two phases represent a significant contribution for the extraction process.

The detailed mechanistic events during ion extraction from an aqueous to an organic phase are not known from the experiment. Three speculative models were proposed: the ionophore partition model, the cation partition model, and the adsorption–desorption model.[5, 60, 61] In the first model the ligand **L** first diffuses from the organic phase to water where it complexes M^+, and then diffuses back to the organic phase. In the second model, an equilibrium between $(M^+)_{wat}$ and $(M^+)_{org}$ is assumed, and involves formation of the $\mathbf{LM}^+$ complex in the organic phase. The third model assumes the adsorption of both **L**, of M^+, and its counteranion at the interface, where the $\mathbf{LM}^+\text{Anion}^-$ complex forms before diffusing to the organic phase. No experimental data discriminate among these models. From our results, no clear argument emerges either concerning the mechanism of extraction. However, the fact that no spontaneous diffusion of the hydrated cation to the organic phase or of the free calix-bis-crown ionophore to water takes places during the simulations, is more consistent with the adsorption model than with the others. Clearly further modeling studies are required and experiments on extraction of cations revisited, with a particular focus on counterion effects and solvent migration from one phase to the other. Potential of mean force calculations, presently under investigations,[77] should allow consistent comparisons of the migration of free and complexed cation, involving counterion effects.

Conclusions

We report a method of theoretical calculations of extraction selectivity based on the FEP technique. It is applied to the calix[4]-bis-crown6 ionophore, **L**, which displays a remarkable extraction selectivity for Cs^+ over Na^+ from an aqueous to a chloroform phase.

Our calculations provide microscopic pictures of the complexes in solution and demonstrate that solvent effects play an important role on the selectivity of *complexation* in pure homogeneous solvent and of *extraction*. We predict that the ligand **L** prefers Na^+ over Cs^+ in chloroform solution (as in the gas phase).[20] In pure water, the selectivity differs markedly: it is predicted to complex Cs^+ better than Na^+.

The extraction of cations from an aqueous to an organic phase is a complicated process, which involves relative solubilities and stabilities of the complexes in the organic phase saturated with water. Experimentally, for calix[4]crown-6[34] and calix[4]-bis-crown-6[29, 34, 36] ionophores, the extraction selectivity from water to chloroform or to (2-nitrophenyl)octylether peaks at Cs^+ ($Cs^+ > Rb^+ > K^+ > Na^+$). It was suggested that this order corresponds to the relative free energies of binding in chloroform.[34] Our results do not support this view, because in dry chloroform, with or without counterion, the largest affinity is calculated for Na^+ as in the gas phase. Conversely, we estimated the extraction selectivity of alkali cations from water to chloroform by the calix[4]-bis-crown ligands, and found that Cs^+ is extracted better than Na^+, in agreement with the experiment.

Finally, we report the first MD simulations concerning the free and complexed calixarene ionophores at a water/chloroform interface. Full migration of the solute from the interface to the bulk organic phase was not observed. The solutes remain adsorbed at the interface like surfactants, despite their different nature. A similar behavior has been observed computationally on related free[78] and complexed ionophores like calix[4]-crown-6[79], the calix[4]arene$^-$ anion[80], CMPO[81] or diamide ligands.[82] This is in agreement with surface tension experiments[83] and interpretation of kinetic data[84] on related macrocyclic compounds. Without picrate counterion, the LCs^+ complex remains an inclusive type, as in pure water or pure chloroform. At the interface, the picrate counterion dissociates from the complex, but also remains adsorbed at the interface, equally shared between the two phases. Such studies are in their infancy, and have to be pursued with methodological (involving consistent representation of the solvents, including polarization effects) investigations, and compared with related ionophoric systems. It is hoped that the microscopic pictures resulting from computer experiments will shed light on the mechanism and energetics of capture and transport of metal cations in the two-phase systems.

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